

BIOGRAPHICAL SKETCH

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NAME: Feng Liu, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): liuf2002

POSITION TITLE: Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Wuhan University, P.R. China	B.S.	1982	Biochemistry
Iowa State University, Ames, Iowa	Ph.D.	1990	Biochemistry
Stanford University, Stanford, CA	Postdoc.	1991-1992	Biochemistry
Stanford University, Stanford, CA	Postdoc.	1992-1995	Mol. Pharmacology

A. Personal Statement

The current project focuses on the roles of the disulfide bond oxidoreductase-A like protein (DsbA-L) in the regulation of mitochondrial function as well as lipid and glucose metabolism in hepatocytes. DsbA-L was originally identified by us as a key regulator of adiponectin multimerization and function in adipocytes (*Liu et al. (2008) Proc Natl Acad Sci U S A. 105, 18302-7*). For the past several years, we have clearly demonstrated that, using various biochemical and cell biology approaches as well as fat-specific DsbA-L overexpression mouse model, DsbA-L plays important roles in regulating the insulin sensitizing effect of adiponectin in adipose tissue (*Zhou et al. (2010) Diabetes. 59, 2809-16; Liu et al. (2012) Diabetes. 61, 2776-86*). The current study is based on several important new findings from our preliminary study: **1)** DsbA-L is highly expressed in the liver and its expression levels are negatively associated with obesity in mice and human subjects; **2)** DsbA-L is localized in mitochondria, interacts with PGC-1 α , and the interaction is negatively correlated with acetylation; and **3)** liver-specific knockout of DsbA-L led to mitochondrial dysfunction, hepatosteatosis, and insulin resistance. Our preliminary studies strongly suggest that DsbA-L plays an important role in regulating mitochondrial function and liver metabolism. Our study is important because it will not only identify a new key regulator of mitochondrial function in the liver, but will also shed light on the potential link between obesity and metabolism disorders in the liver such as hepatosteatosis and insulin resistance.

The focus of my research for over past 20 years has been the mechanisms underlying obesity-induced metabolic diseases such as insulin resistance, inflammation, and type 2 diabetes, focusing on the insulin and adiponectin signaling pathways. I have a strong background in biochemistry, cell and molecular biology, cell signaling, and metabolic physiology. I have extensive and successful experience in developing and administering new research projects, motivating students and postdoctoral fellows, collaborating with other researchers, producing high-quality publications, and have been very productive in all my career development stages. In summary, I have a demonstrated track record of success and productivity in the diabetes research field and I am confident that I will successfully lead and complete the proposed project.

B. Positions and Honors.

Positions and Employment

- 1996-2001 Assistant Professor, Pharmacology, Univ. Texas Health Sci. Ctr at San Antonio (UTHSCSA)
1998-2001 Assistant Professor, Biochemistry, UTHSCSA
2001-2005 Associate Professor with tenure, Pharmacology and Biochemistry, UTHSCSA
2005-present Professor with tenure, Pharmacology and Biochemistry, UTHSCSA

Peer Review Committees:

- NIH Endocrinology Study Section, *ad hoc* reviewer (2000)
NIH Special Emphasis Panel (EMNR IRG) (2003 - 2005)
NIA-B, Biological Aging Review Committee, *ad hoc* reviewer (2003)
VA Endocrinology Merit Review Panel, *ad hoc* reviewer (2004-2006)
American Heart Association, Western Review Consortium, member (2004-2006)
American Diabetes Association Research Review Panel, Member (2004-2010)
NIH IPOD and CADO Study Section *ad hoc* reviewer (2006, 2007)
NIH CADO Study Section; Member (2008-2012)
NIH Special Emphasize Panel, Ad hoc reviewer (2012-present)
NIH CADO Study Section; Ad Hoc reviewer (2015)

Honors

- 1990 Zaffarano Prize Award (Honorable Mention), Iowa State University
1990 Research Excellence Award, Iowa State University
1990 Graduate Student Research Award, Department of Biochem. & Biophys., Iowa State Univ
1996 Lyndon Baines Johnson Research Award, American Heart Association, Texas Affiliate
1997 Howard Hughes Medical Institute New Faculty Award, UTHSCSA
1997 Career Development Award, American Diabetes Association

C. Contribution to Science

1. My early study focused on the mechanisms regulating insulin signaling. By yeast two-hybrid screening using the insulin receptor beta subunit as bait, I have identified for the first time an SH2 protein (called Grb-IR or Grb10) that inhibits insulin signaling. For the past 19 years, we have characterized the roles of Grb10 in regulating insulin signaling and action using both cells and tissue-specific Grb10 knockout mouse models. Our studies have elucidated a novel mechanism regulating insulin signaling and function and identified a potential target for improving insulin action in vivo.
 - a. Liu F, Roth RA (1995) Grb-IR: a SH2-domain-containing protein that binds to the insulin receptor and inhibits its function. *Proc Natl Acad Sci U S A.*; 92(22):10287-91.
 - b. Wick KR, Werner ED, Langlais P, Ramos FJ, Dong LQ, Shoelson SE, Liu F. (2003) Grb10 inhibits insulin-stimulated insulin receptor substrate (IRS)-phosphatidylinositol 3-kinase/Akt signaling pathway by disrupting the association of IRS-1/IRS-2 with the insulin receptor. *J Biol Chem.*; 278(10):8460-7.
 - c. Zhang J, Zhang N, Liu M, Li X, Zhou L, Huang W, Xu Z, Liu J, Musi N, DeFronzo RA, Cunningham JM, Zhou Z, Lu XY, Liu F. (2012) Disruption of growth factor receptor-binding protein 10 in the pancreas enhances β -cell proliferation and protects mice from streptozotocin-induced β -cell apoptosis. *Diabetes.* 61(12):3189-98.
2. Adiponectin has been receiving a great deal of attention due to its potential therapeutic use for metabolic and cardiovascular disorders. Adiponectin, which exists in serum in

three major complexes including trimer, hexamer, and the high molecular weight (HMW) form and different adiponectin complexes exert tissue-specific biological functions and activate distinct signaling pathways. We have identified a protein named disulfide bond oxidoreductase A –like protein (DsbA-L) that regulates adiponectin multimerization and secretion in adipocytes (*Liu et al. (2008) PNAS*). Our work has been evaluated by the Faculty of 1000 as “**an elegant study**” that “*identified a novel regulator for adiponectin maturation and oligomerization...*”. We have demonstrated that DsbA-L protects obesity-induced ER stress and adiponectin down-regulation. We have also shown that fat-specific overexpression of DsbA-L protected mice from obesity-insulin resistance and metabolic dysfunction.

- a. Liu M, Zhou L, Xu A, Lam KS, Wetzel MD, Xiang R, Zhang J, Xin X, Dong LQ, Liu F. (2008) A disulfide-bond A oxidoreductase-like protein (DsbA-L) regulates adiponectin multimerization. *Proc Natl Acad Sci U S A.*; 105(47):18302-7
- b. Zhou L, Liu M, Zhang J, Chen H, Dong LQ, Liu F. (2010) DsbA-L alleviates endoplasmic reticulum stress-induced adiponectin downregulation. *Diabetes*. 59(11): 2809-16.
- c. Liu M, Xiang R, Wilk SA, Zhang N, Sloane LB, Azarnoush K, Zhou L, Chen H, Xiang G, Walter CA, Austad SN, Musi N, DeFronzo RA, Asmis R, Scherer PE, Dong LQ, Liu F. (2012) Fat-specific DsbA-L overexpression promotes adiponectin multimerization and protects mice from diet-induced obesity and insulin resistance; *Diabetes*, 61(11):2776-86.

3. Over the past decade, great progress has been made on our understanding of the anti-obesity benefits of the beige cells and the mechanisms regulating the “beigeing” process at the transcriptional level. However, the upstream signaling pathways and the key regulators involved in the regulation of adipogenesis, thermogenesis, and adipocyte function remain to be fully characterized. We have identified Grb10 as a key regulator of thermogenesis and the beige fat development. In addition, we found that Grb10 exerts its role by negatively regulating mTORC1 through a phosphorylation-dependent mechanism. Our study has received great attention worldwide and has been reported by more than 20 news agencies including *Science Dairy*, *ScienceNewsline*, *ScienceCodex*, *Heath Medicine Network*, *World News*, *Business Standard*, *Jersey Tribune*, and etc. Following are several website-linkers showing the report of our findings: <http://www.scidai.ly/releases/2014/06/140605141944.htm>; http://www.sciencecodex.com/team_finds_onoff_switch_to_burning_stored_fat-135112; <http://www.sciencenewsline.com/summary/2014060519050077.html> http://article.wn.com/view/2014/06/06/Team_finds_onoff_switch_to_burning_stored_fat_The_University/ <http://jerseytribune.com/2014/06/05/team-finds-on-off-switch-to-burning-stored-fat/>

We have also identified several miRNAs involved in regulating the beigeing process.

- a. Liu M, Bai J, He S, Villarreal R, Hu D, Zhang C, Yang X, Liang H, Slaga TJ, Yu Y, Zhou Z, Blenis J, Scherer PE, Dong LQ, Liu F. (2014) Grb10 promotes lipolysis and thermogenesis by phosphorylation-dependent feedback inhibition of mTORC1. *Cell Metab.*;19(6):967-80.
- b. Liu B1, Liu F. (2014) Feedback regulation of mTORC1 by Grb10 in metabolism and beyond. *Cell Cycle*. 13(17): 2643-4.
- c. Kong X, Yu J, Bi J, Qi H, Di W, Wu L, Wang L, Zha J, Lv S, Zhang F, Li Y, Hu F, Liu F, Zhou H, Liu J, Ding G. (2014) Glucocorticoids transcriptionally regulate miR-27b

expression promoting body fat accumulation via suppressing the browning of white adipose tissue. *Diabetes*. 64, 393-404

- d. Hu F, Wang M, Xiao T, Yin B, He L, Men W, Dong M, Liu F. (2015) miR-30 Promotes Thermogenesis and the Development of Beige Fat by Targeting RIP140. *Diabetes*. 64, 2056-68

4. List of Publications in 2014-2015:

- 1) Zhang J, Liu F. (2014) Tissue-specific insulin signaling in the regulation of metabolism and aging. *IUBMB Life*. 66(7):485-95.
- 2) Luo Y, He F, Hu L, Hai L, Huang M, Xu Z, Zhang J, Zhou Z, Liu F, Dai YS (2014) Transcription factor Ets1 regulates expression of thioredoxin-interacting protein and inhibits insulin secretion in pancreatic β -cells. *PLoS One*; 9(6):e99049.
- 3) Fang Q, Yang W, Li H, Hu W, Chen L, Jiang S, Dong K, Song Q, Wang C, Chen S, Liu F, Jia W. (2014) Negative regulation of DsbA-L gene expression by the transcription factor Sp1. *Diabetes*. 2014 Dec;63(12):4165-71.
- 4) Liu B, Liu F. (2014) Feedback regulation of mTORC1 by Grb10 in metabolism and beyond. *Cell Cycle*; 13(17):2643-4.
- 5) Hu F, Liu F. (2014) Targeting tissue-specific metabolic signaling pathways in aging: the promise and limitations. *Protein Cell*.; 5(1):21-35.
- 6) Ou X, Liu M, Luo H, Dong LQ, Liu F. (2014) Ursolic acid inhibits leucine-stimulated mTORC1 signaling by suppressing mTOR localization to lysosome. *PLoS One*; 9(4):e95393.
- 7) Liu M, Bai J, He S, Villarreal R, Hu D, Zhang C, Yang X, Liang H, Slaga TJ, Yu Y, Zhou Z, Blenis J, Scherer PE, Dong LQ, Liu F. (2014) Grb10 promotes lipolysis and thermogenesis by phosphorylation-dependent feedback inhibition of mTORC1. *Cell Metab*.;19(6):967-80
- 8) Kong X, Yu J, Bi J, Qi H, Di W, Wu L, Wang L, Zha J, Lv S, Zhang F, Li Y, Hu F, Liu F, Zhou H, Liu J, Ding G. (2015) Glucocorticoids transcriptionally regulate miR-27b expression promoting body fat accumulation via suppressing the browning of white adipose tissue. *Diabetes*. 64, 393-404
- 9) Zhao L, Tang M, Hu Z, Yan B, Pi W, Li Z, Zhang J, Zhang L, Jiang W, Li G, Qiu Y, Hu F, Liu F, Lu J, Chen X, Xiao L, Xu Z, Tao Y, Yang L, Bode AM, Dong Z, Zhou J, Fan J, Sun L, Cao Y. (2015) *Oncotarget*. 6, 15995-6018.
- 10) Hu F, Wang M, Xiao T, Yin B, He L, Men W, Dong M, Liu F. (2015) miR-30 Promotes Thermogenesis and the Development of Beige Fat by Targeting RIP140. *Diabetes*. 64, 2056-68
- 11) Liu M, Chen H, Wei L, Hu D, Dong K, Jia W, Dong LQ, Liu F. (2015) Endoplasmic reticulum (ER) localization is critical for DsbA-L protein to suppress ER stress and adiponectin down-regulation in adipocytes. *J Biol Chem*. 290(16):10143-8
- 12) Ruan H, Liu F. (2016) Regulation of energy metabolism and maintenance of metabolic homeostasis: the adiponectin story after 20 years. *Journal of molecular cell biology*. 8(2):91-2.
- 13) Cai H, Dong LQ, Liu F. (2016) Recent Advances in Adipose mTOR Signaling and Function: Therapeutic Prospects. *Trends in pharmacological sciences*. 37(4):303-17.
- 14) Hu F, Xu Y, Liu F (2016) Hypothalamic roles of mTOR complex I: integration of nutrient and hormone signals to regulate energy homeostasis. *AJP Endocrinol Metab*. 310(11):E994-E1002.

- 15) Chen, H, Bai, J, Dong, F, Fang, H, Zhang, Y, Meng, W, Liu, B, Luo, Y, Liu, M, Bai, Abdul-Ghani, MA, Li, R, WuJ, Zeng, R, Zhou, Z, Dong, LQ, Liu, F. (2017) Hepatic DsbA-L protects mice from diet-induced hepatosteatosis and insulin resistance. FASEB J. In press.
- 16) Liu, X, Cervantes, C, Liu, F (2017) Common and distinct regulation of human and mouse brown and beige adipose tissues: a promising therapeutic target for obesity. Protein & Cells. In press.
- 17) Meng, M, Liang, X, Chen, H, Luo, H, Bai1, J, Li, G, Zhang, Q, Xiao, T, He, S, Zhang, Y, Xu, Z, Xiao, B, Liu, M, Hu, F, and Liu, F (2017) Rheb Inhibits Beigeing of White Adipose Tissue via PDE4D5-dependent Down-regulation of the cAMP-PKA Signaling Pathway. Diabetes. In press.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/12SXa5t2bFs5C/bibliography/47390382/public/?sort=date&direction=ascending>

D. Research Support

Ongoing:

R01 DK100697; 07/13/2013 – 06/30/2017; PI: Liu, F.

Regulation of Adipose Tissue Function by Grb10.

The major goal of this study is to study the regulation of mTOR signaling and adipose tissue function by Grb10.

R01 DK076902; 04/01/14-03/31/2018; PI: Liu, F.

Regulation and Function of Adiponectin Oligomerization.

The major goal of this study is to characterize the roles of DsbA-L in the regulation of adiponectin multimerization, insulin sensitivity, and energy homeostasis in adipose tissue.

Completed during the last three years:

American Diabetes Association 1-12-BS-115 01/01/2012-12/30/2015, PI: Liu, F.

The roles of DsbA-L in adiponectin multimerization and function in vivo.

The major goal of this study is to characterize the in vivo role of DsbA-L in adiponectin biosynthesis and function.

R01 DK 5R01DK076902-02; 04/01/08-01/31/13 NIH/NIDDK, PI: Liu, F.

Regulation and Function of Adiponectin Oligomerization

The major goal of this study is to characterize the regulatory mechanism and function of adiponectin oligomerization

Pending:

R01 DK114479; 07/01/2017 - 06/30/2022 PI: Liu F

Regulation of Mitochondrial Biogenesis and Function by DsbA-L in the Liver

R01 DK115761 12/01/2017 - 11/30/2022 Multi-PI: Liu F and Xu Y

Hypothalamic Grb10 and body weight

R01 DK100697 12/01/2017 - 11/30/2022 PI: Liu F

Regulation of Adipose Tissue Function

Project Description (Liu lab -2017)

There has been a great interest over the past decade in understanding the mechanisms controlling the formation and function of brown adipose tissue (**BAT**) and the development of beige fat, because improved brown and beige fat function may have great metabolic benefits including prevention of over-nutrition-induced obesity and increasing insulin sensitivity.

Cold-induced adaptive thermogenesis in BAT is mediated principally by norepinephrine discharged from the sympathetic nerve terminals. Impressive evidence has accumulated over the past few years to suggest that activation of beige fat, which is less innervated, could be stimulated by norepinephrine released from macrophages that are alternatively activated by a thermogenic circuit consisting of eosinophils and interleukin (**IL**)-4/13. Beige fat development and thermogenesis can also be induced by IL-33 induced-activation of Group 2 innate lymphoid cells (**ILC2s**), which activate the eosinophils-IL4/13 pathway or by secretion of methionine-enkephalin peptides. However, it is unknown whether additional mechanism(s) exist that act independently or cooperatively with the IL-4/13 pathway to mediate environmental change-induced beige fat development and thermogenesis.

We recently showed that fat-specific knockout of Rheb greatly increased beige fat thermogenesis via an mTORC1-independent mechanism (*Meng et al (2017) Diabetes, In press*). While we found that Rheb knockout promoted protein kinase A (**PKA**) signaling and consequent UCP-1 expression by down-regulation of phosphodiesterase-4D5, we also detected a significant increase in miR-182-5p levels in white adipose tissue (**WAT**) of the fat-specific Rheb knockout mice (Rheb^{ko}). This result is very interesting because adipose miR-182-5p levels are significantly stimulated by cold exposure and knockout of miR-182-5p suppressed cold exposure-induced thermogenesis in mice. More interestingly, overexpression of miR-182-5p significantly promoted UCP-1 expression in primary adipocytes when the cells were co-cultured with macrophages. Based on these novel findings, we hypothesize that **up-regulation of miR-182-5p mediates cold-induced beige fat thermogenesis and improves metabolic function via a macrophage-dependent mechanism**. To test this hypothesis, we propose the following specific aims:

Specific Aim 1. To determine the physiological roles of miR-182-5p in beige fat thermogenesis and metabolic homeostasis *in vivo*. We will determine: 1) to what extent miR-182-5p contributes to Rheb deficiency-induced beige fat thermogenesis; 2) if knocking out or overexpression of miR-182-5p reduces or increases, respectively, insulin sensitivity and metabolic homeostasis in diet-induced obese mice; and 3) whether and how up-regulation of miR-182-5p alleviates obesity-induced inflammation in mice.

Specific Aim 2. To elucidate the mechanisms underlying miR-182-5p-induced beige fat thermogenesis. Our preliminary data showed that overexpression of miR-182-5p had no effect on UCP-1 expression in primary adipocytes, but significantly increased UCP-1 expression when the primary adipocytes were co-cultured with macrophages. Taken together with the finding that overexpression of miR-182-5p significantly stimulated the expression of IL-10, a well-established inducer of alternative activation of macrophages, we hypothesize that miR-182-5p promotes beige fat thermogenesis by IL-10-mediated alternative activation of macrophages. To test this hypothesis, we will determine: 1) if miR-182-5p mediates cold-stimulated thermogenesis by promoting alternative activation of macrophages *in vivo*; 2) if IL-10 mediates the stimulatory roles of miR-182-5p in M2 macrophage activation and thermogenesis; and 3) if the miR-182/IL-10 signaling pathway acts independently or cooperatively with the IL-4/13 pathway in mediating cold-induced beiging of WAT and thermogenesis.

Specific Aim 3. To characterize the target of miR-182-5p in regulating IL-10 expression and thermogenesis. By bioinformatics algorithm profiling, DNA microarray analysis as well as biochemical studies, we have identified the MHC class II transcription coactivator (**CIITA**) as a promising target of miR-182-5p in adipocytes. Taken together with the findings that CIITA negatively regulates IL-10 expression in several cells including adipocytes, we hypothesize that miR-182 may promote IL-10 expression and thermogenesis in adipose tissue by down-regulation of CIITA. To test this hypothesis, we will determine: 1) if CIITA gene is a direct target of miR-182 in adipocytes; 2) if CIITA deficiency increases IL-10 expression and thermogenic gene expression *in vivo*; and 3) if fat-specific overexpression of CIITA inhibits cold-induced thermogenesis *in vivo*.